PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4084PTWO/AG/a	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/051263	International filing date *(day/month/year)* 28.06.2004	Priority date *(day/month/year)* 30.06.2003
International Patent Classification (IPC) or national classification and IPC C07D333/56		
Applicant ERREGIERRE S.P.A. et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 5 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.04.2005	10.06.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer De Jong, B Telephone No. +31 70 340-2833

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/051263

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-10 as originally filed

   Claims, Numbers

   1-24 received on 09.05.2005 with letter of 28.04.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19
	No:	Claims	20-24
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-24
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V.

The following document is referred to in this communication:

D1 : EP 0 062 503 A (LILLY CO ELI) 13 October 1982 (1982-10-13)

D2: US-A-4 418 068 (JONES CHARLES D) 29 November 1983 (1983-11-29)

Added Matter

The amendments filed with the International Bureau under Article 19(1) introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 19(2) PCT:

In the new claim 1, stage (d2) is now conducted directly on the reaction mixture derived from stage (d1). Although the wording is literally taken from claim 12, the teaching is not the same. In original claim 12 stage (d2) is conducted directly on the reaction mixture derived from stage (d1), **but only after water and ethyl acetate have been added** to this reaction mixture. From the wording in the new claim 1, the skilled person would understand that the concentrated hydrochloric acid is added to the reaction mixture without doing anything else with the reaction mixture. Since this possibility was not explicitly disclosed in the original application, subject-matter has been added. The examination of claim 1 has therefore been carried disregarding the amendment.

Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 20-24 is not new in the sense of Article 33(2) PCT:

It is well a well established principle that, in general, a document disclosing a low molecular chemical compound and its manufacture make this compound available to the public in all grades of purity. This means that the purity of a compound cannot confer novelty in cases where the compound is already disclosed in the prior art, even if the prior art processes do not lead to the compound with the desired purity.

The reason for this is that the compound with the desired purity can be obtained using conventional methods for purification (see e.g. T 990/96 (OJ EPO 1998, 489)). Raloxifene hydrochloride with a very high purity can be easily obtained using (for instance) HPLC. Document D1 is therefore novelty destroying for claims 20-22. For the same reasons the compound with particular particle sizes (which can be obtained by conventional grinding and sieving) is also considered as being anticipated by D1. Document D1 is therefore novelty destroying for claims 23,24.

The present application relates to a process for preparing raloxifene hydrochloride (I) via intermediates (II), (III), (IV), (V) and (VI). This process is novel over the process disclosed in D1 (see preparations 1,5 and examples 2,6) due to the fact that acidification (stage d2) is carried out in the present application using concentrated HCl instead of 50% aqueous methanesulfonic acid in D1. Example 6 of D1 results therefore in the formation of the methanesulfonate salt, which is subsequently treated with ammonia in order to prepare the free base (the yellow foam mentioned in the present application when discussing D1). Therefore the subject-matter of claims 1-19 is novel.

Non-Unity

The products according to claims 20-25 (with the specified purity and particle sizes) are not the result of the process according to claim 1. They are only formed after conventional crystallisation methods and sieving of the compounds. Thus they do not share any special technical feature with the claimed process as is required by Rule 13(2) PCT.

The applicants argument that the product claimed in claim 20 is strictly correlated to the processes according to claims 1-19 is not very relevant. It is noted that the applicant does not mention in his arguments which common feature could be regarded as the "special technical feature" within the meaning of Rule 13(2) PCT.

Inventive step

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-19 does not involve an inventive step in the sense of Article

33(3) PCT:

In D1 (closest prior art) raloxifene hydrochloride (I) is prepared e.g. by the process disclosed in example 17 of D1, were the free base raloxifene is treated with HCl gas. (It is noted that according to D1 the starting material is the benzoyloxy compound according to example 3, but it appears from the identical example 15 in D2 that the starting material is probably the free base)

In view of this prior art, the problem was to provide an alternative process for the preparation of raloxifene hydrochloride.

On page 41, lines 13-16 the deprotection of compounds with -COR^6 groups is discussed. It is said that the hydrolysis is readily carried out with acid catalysts such as methanesulfonic acid, hydrochloric acid, hydrobromic acid..... etc.

In order to solve the problem stated above, the skilled person therefore would use the process according to preparations 1,5 and examples 2,6 in D1 (already discussed under point 2) and use concentrated hydrochloride instead of the 50% aqueous methanesulfonic acid solution. He would thus come to the process of the present application without an inventive step.

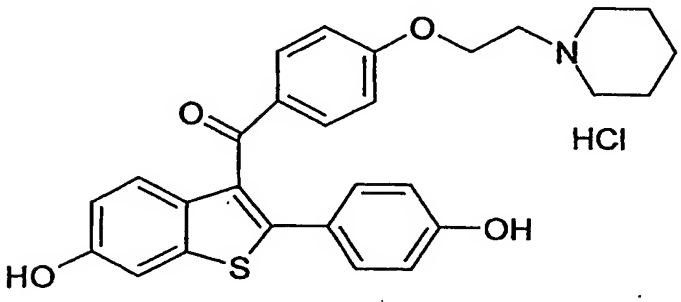
Dependent claims 2-19 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (Article 33(3) PCT).

The applicants arguments concerning inventive step have been carefully considered, but most of these arguments are based on a more ambitious problem than the the problem used in our analysis. According to the applicant the problem was to obtain raloxifen hydrochloride with a very high purity degree and a very low content of aluminium impurities. However this problem cannot be accepted since it is not credible that this problem is solved by the process of claim 1 **over the whole claimed range**. (In this respect it is also noted that carrying out the process according to claim 1 results in a crude reaction mixture and not in the formation of pure raloxifen hydrochloride). It therefore

seems that the features according to dependent claims 11-13 are essential features in case the problem is the more abitious one. A claim in which the features of claims 1,11,12 and 13 are combined would be considered as inventive.

CLAIMS

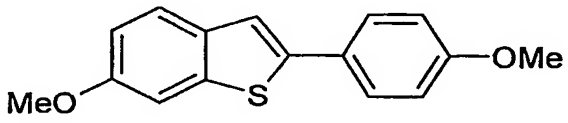
1. Process for preparing raloxifene hydrochloride of formula (I)



(I)

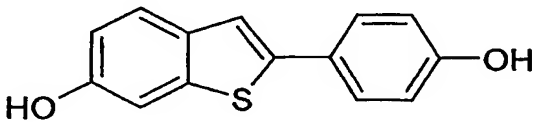
with a purity higher than 98% comprising the following stages:

a) demethylation of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene of formula (II)



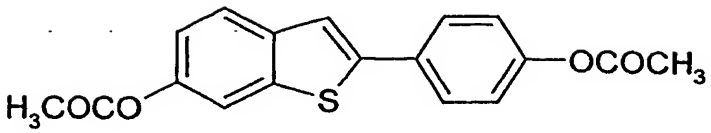
(II)

in pyridine hydrochloride to obtain 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene of formula (III)



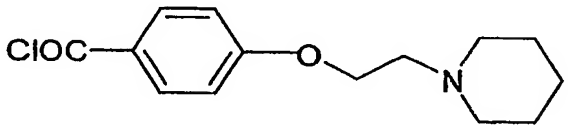
(III)

b) acetylation of 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene with an acetylating agent to obtain the corresponding 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene of formula (IV)



(IV)

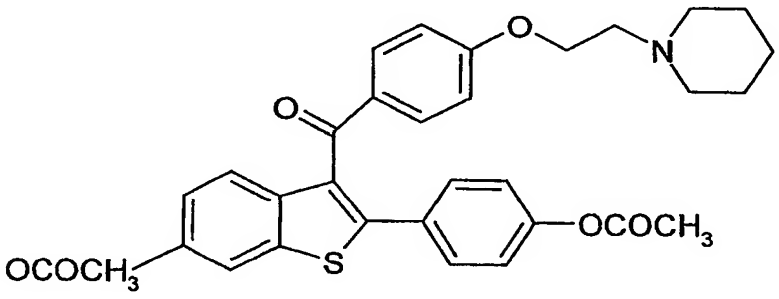
c) acylation of 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) with 4-(2-piperidinoethoxy)benzoylchloride hydrochloride of formula (V)



HCl

(V)

with aluminium chloride in halogenated solvent to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene of formula (VI)



(VI)

d) hydrolysis of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene, according to the following operative modalities:

d1) treatment of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene with alkaline hydroxide in alcohol solvent,

d2) acidification of the product obtained in the preceding stage (d1) with a strong

acid, to obtain the corresponding raloxifene salt with the strong acid, characterised in that the strong acid used in stage (d2) is concentrated hydrochloric acid and said stage (d2) is conducted directly on the reaction mixture derived from stage (d1) .

2. Process as claimed in claim 1, characterised in that the pyridine hydrochloride used in stage (a) is prepared in situ by adding concentrated hydrochloric acid to pyridine and distilling off all the water to obtain a thick but stirrable residue.

3. Process as claimed in claim 1 or 2, characterised in that the demethylation reaction or stage (a) of the process of the present invention is also conducted in the presence or tributylamine.

4. Process as claimed in claim 3, characterised in that tributylamine is used preferably in weight ratios with respect to 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (II) of between 0.5 and 2.

5. Process as claimed in claim 4, characterised in that stage (a) is conducted at a temperature between 170 and 180°C.

6. Process as claimed in any one of claims 1-5, characterised in that acetic anhydride is used as acetylating agent in the presence of triethylamine in ethyl acetate.

7. Process as claimed in any one of claims 1-6, characterised in that the 4-(2-piperidinoethoxy)benzoylchloride hydrochloride of formula (V) used in stage (c) is prepared in situ, by reacting 4-(2-piperidinoethoxy)benzoic acid hydrochloride with thionyl chloride in methylene chloride in the presence of pyridine, without isolating the reaction product.

8. Process as claimed in any one of claims 1-7, characterised in that stage (c) is conducted in methylene chloride.

9. Process as claimed in claim 8, characterised in that stage (c) is conducted according to the following operative modalities: 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) is added to non-isolated 4-(2-piperidinoethoxy)benzoylchloride hydrochloride of formula (V) and prepared in situ as in claim 7 and the aforesaid mixture is poured onto a mixture consisting of methylene chloride and aluminium trichloride.

10. Process as claimed in any one of claims 1-9, characterised in that the 6-

acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) is not isolated, but is used in the crude state in the subsequent reaction (d).

11. Process as claimed in any one of claims 1-10, characterised in that stage (d1) is conducted using methanol as alcohol solvent and excess 30% sodium hydroxide.

12. Process as claimed in any one of claims 1-11, characterised in that stage (d2) is conducted directly on the reaction mixture derived from stage (d1) to which are added equal weight quantities of water and ethyl acetate and finally 37% concentrated hydrochloric acid.

13 Process as claimed in claim 1-12, characterised in that the suspension obtained in stage (d2) is washed with equal weight quantities of water and ethyl acetate.

14. Process as claimed in any one of claims 1-13, characterised in that raloxifene hydrochloride has an HPLC purity >98%.

15. Process as claimed in any one of claims 1-14, characterised in that raloxifene hydrochloride derived from stage (d2) is crystallised from an alcoholic solvent.

16. Process as claimed in claim 15, characterised in that said solvent is methanol possibly in the presence of HCl.

17. Process as claimed in any one of claims 15 and 16, characterised in that raloxifene hydrochloride is obtained with a purity greater than 99%.

18. Process as claimed in any one of claims 15 and 16, characterised in that a further crystallisation from raloxifene hydrochloride from alcohol solvent is conducted.

19. Process as claimed in claim 18, characterised in that said crystallisation is conducted in methanol possibly in the presence of HCl.

20. Raloxifene hydrochloride with a purity greater than 99.7% and containing aluminium in a quantity less than 5 ppm %.

21. Raloxifene hydrochloride as claimed in claim 20 characterised in that it contains raloxifene hydrochloride N-oxide in a quantity less than 0.05%.

22. Raloxifene hydrochloride as claimed in claim 21, characterised in that said impurity is contained in a quantity less than 0.01%.

23. Raloxifene hydrochloride as claimed in any one of claims 20-22, characterised

by having a D(0.9) ≤100µm and a D(0.5) ≥40µm.

24. Raloxifene hydrochloride as claimed in claim 23, characterised, after a further sieving, by having a D(0.9) between 50 and 65 µm and a D[4.3] ≥20µm.